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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,149	02/05/2004	George N. Cox III	4152-1-PUS-5	7193

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EXAMINER	
STOICA, ELLY GERALD	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 08/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,149	COX, GEORGE N.	
	Examiner	Art Unit	
	Elly-Gerald Stoica	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 24-52 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 24-52 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 02/05/2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on February 5, 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Priority

2. Applicant's claim for the benefit of to a prior application 60/052,516 07/14/1997 is acknowledged.

Status of the claims

3. Currently, claims 1-23 have been cancelled by the applicant and claims 24-52 are pending in the application.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 24-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter that was

not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to a genus of granulocyte colony-stimulating factor (G-CSF) insertion variants described as having a cysteine residue inserted between certain amino acid residues and having an in vitro ability to induce G-CSF induced cell proliferation.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In the present case, the Applicant has provided a structural limitation (insertion of cysteine between of certain pairs of amino acids within G-CSF protein) and a functional limitation (the cell proliferation requirement). The Cysteines are needed for PEGylation of the modified growth factor for increase of the half-life of the insertion variants of the G-CSF claimed. The state of the prior art is adequate for the conceptual construction of cysteine mutants or PEGylated growth factors (Cunningham and Wells, Science 244, 1081-1085, Goodson and Katre, Biotechnology 1990, 343-6). Even though the relative skill existent in the art at the time of the priority date claimed would permit the making of

certain cysteine mutants for Growth Hormone (US Pat. 6,608183), in the specification no data are presented as to mutants formed by substitution of amino acid residues with cysteine residues in the structure of the G-CSF. There are teachings in the art that underscore the uncertainty in protein modification in general and in the effects of modifying any particular residue in a protein sequence absent specific teachings relating the amino acid to the protein's function and structure (Bowie et al., Science 247, 1306-131). In the specification, the Applicant proposes "rules" for the modification of the target proteins, members of the Growth Hormone super family, (pages 11 and 12 of the specification) with three key components.

First, the specification identifies as preferred sites for modification those regions of the Growth Hormone supergene family corresponding to the pre-Helix A region, and the region distal to the last helix of the protein, and the A-B, the B-C, the C-D loops (i.e. the loop regions) of the proteins (page 10, lines 10-28 and page 11, lines 14-17)
Second, the application additionally indicates that N- and 0- glycosylation sites may also be preferred sites for protein modification (page 11, lines 19-22). Finally, the application teaches that these rules may be applied to other proteins, and that in such other proteins the amino acids that can be replaced with cysteine without significant loss of "biological activity", as is the insertion of cysteine between two amino acids that are situated in the "disclosed" regions (p11, lines 18-19). It is also noted that the application and the claims include as potential modification sites the first three and the last three residues in each of the A, B, C, and D helices (page 3, lines 3-20 and claim 26),

although the application does not refer to these regions in the description of the "rules" on pages 11 and 12.

It is noted that, "where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed" In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973). Thus, where there is uncertainty in the art, even the presence of multiple species within a claimed genus does not necessarily demonstrate possession of the genus. In the present case, the state of the art has provided a good deal of evidence supporting a finding of uncertainty in the art. However, the application provides only the teachings of the indicated "rules" to support the present claims to the genus. The rules and disclosed species are not deemed sufficient to overcome the uncertainties in the art. Several teaches in the art demonstrate that:

-modification of certain amino acids found within the pre-alpha helix region of the protein results in loss of protein activity;

-amino acid deletion is not predictive of the effects of substitution modifications to the same residues;

-insertion of cysteine has a greater likelihood of disrupting protein structure.

Thus, significant evidence of uncertainty has been presented. The embodiment described in the specification and claimed is rather a prophetic one based on predicted results rather than work actually conducted or results actually achieved.

The strongest contradiction between the teachings in the art and the applicant proposed "rules" are the teachings of Shaw (U.S. 5,166,322) and Zurawski et al (EMBO Journal 12: 5113-5119). The last reference demonstrates that many "unimportant residues" in the GH superfamily protein IL-2 were intolerant to cysteine modifications. It is noted that an alignment of the IL-2 reference in Figure 1 of Zurawski with the structural teachings of IL-2 found in Bazan et al., (Science 257: 410-13) indicates that the A, B, C, and D helices of the portion of IL-2 correspond, respectively, to the following residues of the Figure 1 sequence: A, R41 (only the C-terminal residue of this helix shown); B, K.68-187; C, N99-K1 12; and D, V130-5142 (all of D helix not shown). Taking into consideration the teachings of the Bazan reference, the Zurawski reference indicates that certain residues found in the A-B loop, the last three residues of each of the A and C helices, and in the first three residues of the C helix are found among those residues described as intolerant to cysteine substitutions. Thus, the reference supports the assertion that those in the art would not be able to predict, based on the teachings in the prior art, which amino residues would be tolerant to cysteine modification according to the teachings of Braxton (US patent 5,766,897). However, these same teachings also demonstrate that cysteine substitutions may not be made freely among the residues in various regions identified by the first "rule" presented in the application. Moreover, in view of the proposed cysteine insertions, the residues F13, L71, L92, I95, would be part of the amino acid pairs in which cysteine insertion are proposed but the insertion have the potential to disrupt the leucine rich hydrophobic network and the protein, and, if obtain will lack stability (Fujii et al, FEBS letters, **410**, p.131 Scheme 1). According to

the same source, the proposed Cysteine insertion in the prehelix A of hG-CSF would severely impair the stability of the protein (Fujii et al, FEBS letters, **410**, p.135, Fig. 3). In view of these teachings, it appears that the application of the Applicant's first rule would still result in uncertainty in the operability of any particular G-CSF variant.

The second "rule" provided by the application is similarly contradicted by the teachings of the Shaw reference. This reference "found that the glycosylation site in IL-3 (asparagine 15) is not useful for creating cysteine mutants in IL-3 because the mutant protein is not biologically active." IL-3 is also among the proteins identified in the application as a member of the GH superfamily. Thus, the teachings of this reference also demonstrate uncertainty in operability of protein variants even upon the application of the second rule. Moreover, the art, and in particular Zurawski, indicate that the effect of the cysteine substations varies with amino acid being substituted. For example, residue 42 (in the A-B loop) of IL-2 was indicated to be intolerant to cysteine substitution, whereas the substitution of amino acids 43 and 44 had relatively little effect on the protein activity. Consequently, Shanafelt and Kastelein, show that (table 1) one cannot predict the activity of the mutant before testing it (Shanafelt A.B., Kastelein, R.A.-Proc. Natl. Acad.Sci. **86**, p4872). For example, the mutants C85S and C93S in the mGMCSF, corresponding to the positions E93 (the last amino acid in the B helix) and L103 (the first amino acid in the C helix) in human G-CSF, have no activity, in contrast to the "rules". Another residue suggested by the "rules" A91 of hG-CSF, when mutated, leads to a biologically inactive mutant (Kuga et al., Biochem. Biophys. Res. Commun. **159**, p.103). While the claims include both structural and functional requirements, the

teachings of the Zurawski, Shanafelt and Kuga references indicate that the structural requirements fail to correlate with the functional requirements. In view of the lack of correlation between the structures and functions relied on to describe the claimed genus, and the evidence of uncertainty in the operability of any particular species of the claimed invention, even upon the application of the "rules", the teachings of the application are not deemed sufficient to provide descriptive support for the claimed genus of G-CSF variants, without undue experimentation needed to obtain the particular bio-active G-CSF insertion mutants.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The Applicant is encouraged to provide any evidence to demonstrate that the disclosure enables the claimed invention.

Conclusion

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elly-Gerald Stoica whose telephone number is (571) 272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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